

## INTRODUCTION TO THE 13TH L.H. GRAY CONFERENCE, 1986

### Free radical biochemistry, radiation injury and Brunel

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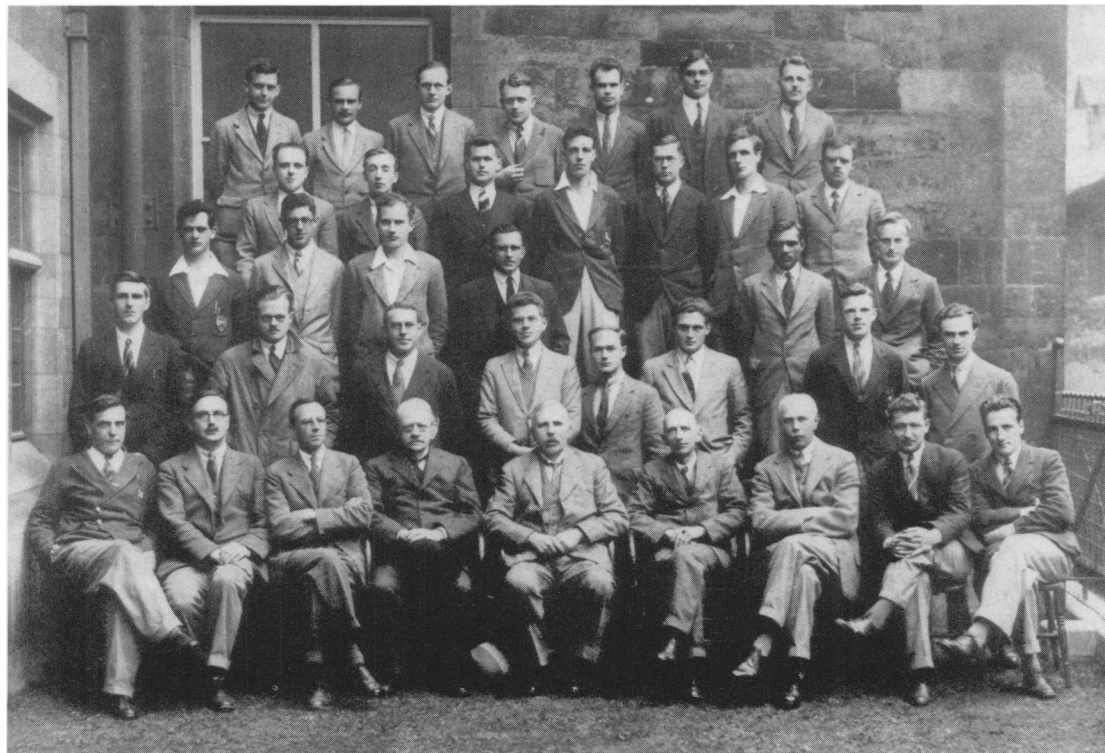
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Brunel University is very pleased to be able to host the 13th L.H. Gray Conference. Although the University's position, within easy reach of central London and just a short taxi journey from Heathrow airport, means that it is often asked to accommodate a wide variety of outside meetings, the hosting of this Gray Conference on the campus is particularly pleasurable, not least because of the University's long association with the nearby Gray Laboratory.

For many of those participating, this will be their first Gray conference. For others this will be their first visit to Brunel. For some this will be their first real introduction to either free radical biochemistry or radiobiology. Let me begin then with a few words about each of these in turn.

The Gray Conferences are organised by the L.H. Gray Memorial Trust set up in 1967 by the British Institute of Radiology, the Association for Radiation Research and the Hospital Physicists Association to honour the memory of Dr Gray. The Conferences are held at approximately 2 yearly intervals on various subjects in radiation sciences and related areas. Examples of Conferences with a biochemical leaning were those held at the University of Sussex in 1973 (Adams *et al.*, 1975), and at the University of Cambridge in 1977 (Adams *et al.*, 1978).

Dr Gray, whose name has since been adopted as the international unit of radiation dose ( $1 \text{ Gy} = 1 \text{ J kg}^{-1}$  or 100 rads) studied physics at Cambridge graduating in 1927 (Hewitt, 1966). Below is a copy of a photograph presently displayed in the Gray Laboratory showing Rutherford, J.J. Thomson and many of the other well known physicists of the time (Figure 1).



**Figure 1** From left to right: *Back Row:* H.C. Webster, H.S.W. Massey, E.T.S. Walton, G.T.P. Tarrant, J.D. McGee, N.A. de Bruyne, L.H. Gray. *Fourth Row:* J. McDougall, J.P. Gott, W.A. Macky, E.C. Pollard, B.W. Sargent, E.C. Bullard, F.A.B. Ward. *Third Row:* J.E.R. Constable, T.E. Stern, H.O.W. Richardson, J.E.I. Cairns, R.M. Chaudri, G.C. Laurence. *Second Row:* L.G. Vedy, W.L. Webster, H.A. Roberts, M.L. Oliphant, T.E.A. Allibone, W. Riezler, P.B. Moon, C.E. Wynn-Williams. *Front Row:* P. Kapitza, C.D. Ellis, J. Chadwick, Prof. Sir J.J. Thomson, Prof. Sir E. Rutherford, Prof. C.I.R. Wilson, F.W. Aston, J.D. Cockcroft, W.H. Watson.

Brunel University, named after the famous railway and marine engineer was founded in 1966 and is primarily a technological university specialising in engineering and the applied and human sciences. It is unique amongst British universities in that all its undergraduates undertake three 5-month periods of industrial training in outside employment during their four-year course. Over the years many Brunel students have spent one of these training periods undertaking radiation or free radical research at institutions such as the Gray Laboratory, the Cyclotron Unit Hammersmith, the Hahn Meitner Institut West Berlin, the University of California San Diego, Rutgers University New Jersey or CERN Geneva. This cooperation has been greatly appreciated and has helped to make Brunel students often the most successful in the UK in obtaining employment on graduating.

Of the 18 permanent academic staff in the Departments of Biochemistry and Applied Biology, 8 are actively involved in research related to free radicals and/or radiation effects including studies of cancer, heart disease, liver injury, lipid peroxidation, prostaglandin metabolism and inflammation. Julie Denekamp from the Gray Laboratory is a visiting professor and close contact is also maintained with the adjoining chemistry department where Peter Wardman of the Gray Laboratory has a similar appointment. Thanks to bodies such as the Cancer Research Campaign, the Wellcome Foundation, the British Heart Foundation and the Arthritis and Rheumatism Council, the departments have also been able to attract a large number of post graduate students and research fellows who have contributed enormously to the department's research output.

Radiation studies, particularly on radiosensitizing and radioprotective compounds such as metronidazole (Flagyl), glutathione, ascorbate and vitamin E and on processes related to free radical mediated tissue injury, particularly the role of iron, have been undertaken at Brunel since 1973. At this time thanks to the valuable support of Professor Jack Boag and of Professor Richard Norman, then of the University of York, the Biochemistry Department obtained the 4MeV linear accelerator previously used in the Radiotherapy Department at Mount Vernon Hospital. With financial assistance from the Cancer Research Campaign a special radiation laboratory was built and the accelerator refurbished for research. Recently, thanks to the further valuable support of Ged Adams and additional backing from the Cancer Research Campaign, the radiation laboratory has been enlarged and is now linked to a 2,000 Curie cavity-type cobalt source provided by the Medical Research Council. A Bruker ESR spectrometer and a flow cytometer have also been recently acquired.

And so to free radical biochemistry and radiation injury. In the context of this meeting radiation refers to ionising radiation and by definition free radicals are inevitably formed in exposed systems. Indeed, all the chemical and biological changes caused by irradiation must stem from these very first chemical events. A new student entering radiobiology could, therefore, be forgiven for believing that free radical biochemistry must have always been an integral part of radiobiology. In fact, until the late 1960s the subjects led almost separate existences. For historical reasons radiobiological thinking had, not surprisingly, been strongly influenced by physicists. It was perhaps they who gave the strongest support to a statistical model involving the probability of one or more ionisations occurring in a vital molecule, the so-called 'target' theory, to explain the shapes of survival curves, the relationship between biological effect and radiation dose. And it was physics that could explain how, because of the different spatial distributions of the initial ionisations, similar doses of different types of radiation produced different effects. As many of the speakers at this meeting will probably make clear, such concepts do have a place in radiobiology provided the role of subsequent free radical events and the associated biochemistry are taken into account (see Alper, Elkind and Lett and subsequent discussion).

Interestingly, it was perhaps the first observations of the hydrated electron in irradiated water by Keene, Hart and Boag in the early 1960s and the First Gray Conference in 1967 that was to mark the beginning of free radicals and biochemistry playing a more central role in radiobiology. Much of that first conference (held at Mount Vernon Hospital, Northwood, adjacent to what is now the 'Gray Laboratory'), focussed on the fact that, a hitherto unrelated collection of organic compounds could as predicted from free radical chemistry studies, sensitize hypoxic cells to radiation induced killing. The work of Howard Flanders, Bridges, Ged Adams and colleagues stemming from this period and the development of the hypoxic radiosensitisers metronidazole (Flagyl) and misonidazole, which were to be eventually investigated in the clinic, is now well documented (see Adams *et al.*, 1978 and Willson, 1981 and references cited). The associated surge of interest in the free radical chemistry of biological molecules was reinforced considerably by the large amount of valuable kinetic information coming from the newly developed pulse radiolysis technique.

However, it was the report of the characterisation of the enzyme superoxide dismutase (SOD) in 1969 that was to really open up new vistas (McCord & Fridovich, 1969; Fridovich, 1982). Not only had radiation biologists tended to neglect free radicals up to this time, so had biochemists. How could such short lived highly reactive species be at all relevant to the biological cell, was the commonly held view. SOD was to change all that. Here was an enzyme that reacted with a free radical: a protein that could actually be purified and characterised. From now on, radiation chemists and free radical biochemists

were to often work closely together and two particularly stimulating meetings were held in Pinawa, Canada in 1977 and Austin, Texas in 1980 (Singh, 1978; Rodgers & Powers, 1981). Contact between many radiation biologists and free radical biologists however, remained very limited, in spite of the remarkable advances being made in both fields and the likely considerable overlap of interest.

It was in this light that the idea of having a Gray Conference, where established researchers in both radiobiology and free radical biochemistry could come together and discuss the current exciting advances in their individual fields, was first mooted some five years ago. Although since that time this idea has been somewhat overtaken by other events, such as the setting up in 1982 of the Society for Free Radical Research for the interdisciplinary discussion of free radicals and the holding of an international meeting on Radioprotectors and Anticarcinogens in Washington in the same year (Nygaard & Simic, 1983), it was, nevertheless, felt very worthwhile to organise such a meeting. It was thought that this would be particularly so if the meeting was kept relatively small, authoritative speakers were chosen, plenty of time was set aside for discussion and all the meeting was recorded and published as near as possible verbatim. To this end, the present programme was arranged. Each of the speakers has been asked to introduce the highlights of current research in their area of expertise in as didactic a fashion as possible.

In free radical biochemistry the significance of the superoxide radical  $O_2^{\cdot -}$  as a damaging species itself or as a precursor of the hydroxyl radical  $OH^{\cdot}$  particularly with respect to inflammation, reperfusion injury cell transformation and radiation damage continues to attract much discussion (see papers by Lunec, Bulkley, Borek and Petkau). Although radiation chemists have known for a long time that its rate of reaction with most biological molecules is considerably slower than that of the hydroxyl radical  $OH^{\cdot}$ , the possibility that it can be biologically more important in causing critical damage, cannot be ruled out. A low rate of reaction does not necessarily imply a lower efficiency in causing damage: a higher reactivity can sometimes result in a larger number of insignificant reactions. In this context the possibility that what has been variously described as 'decompartmentalised', 'free' or 'low molecular weight chelatable' iron can act as a catalyst and promote the formation of  $OH^{\cdot}$  by what has become to be known as the iron catalysed Haber-Weiss reaction (iron III is first reduced by superoxide and the iron II consequently reacts with hydrogen peroxide in the well known Fenton reaction), has also attracted considerable support (see Willson, 1982, and papers by Bulkley and Ward). Indeed, there is now considerable industrial interest in developing iron chelating agents as adjuvants in the treatment of inflammation and aspects of chemical and ischaemic induced injury. The dangers are obvious, however. Iron has an important role in normal metabolism and there is the additional possibility that in some instances it could protect against superoxide or peroxy radical-induced damage. Iron removal, rather than protecting, might in some circumstances, therefore, result in increased damage (Mondon, 1985).

In radiobiology, of course, the Chernobyl disaster and the possibility that extraneous radiation associated with the nuclear power industry can cause an increased incidence of leukaemia in surrounding areas, has dominated all other matters. In the UK a government committee chaired by Sir Douglas Black concluded that on the basis of current radiobiological evidence, documented radioactive emissions could not be responsible for the suggested 'leukaemia clusters' in the vicinity of the Sellafield reprocessing plant. The possibilities remain therefore that the apparent clusters are either statistical quirks or are due wholly or partly to other factors. An alternative argument has been that the estimated radiation exposures have been underestimated or that the radiobiological methods used for assessing the leukaemia risk are erroneous. The possibility of the latter and doubts concerning current estimates of the radiobiological effectiveness of exposure to high LET radiations at low dose rate, the so-called 'inverse dose rate effect' will clearly be the subject of much future debate (see papers of Adams and Borek and discussion following).

And so to the Conference proper. My apologies for having to blow Brunel's trumpet a little loud in my introduction. Regrettably in these highly competitive times when British University Departments are expected by the government to run as competitive businesses it's a question of actively displaying your wares or die. Excellence in research and respected scientific publications are apparently no longer sufficient. We at Brunel are indeed fortunate in having the excellent radiation and other facilities that we do. These together with stimulating research and teaching and the opportunity to meet and entertain new and old colleagues at Conferences such as these, enables us to keep our spirits high.

We trust you will enjoy your stay at Brunel, your visits to London, our associated Management College at Henley and the nearby Thames Valley. We are indeed glad to be able to host this 13th L.H. Gray meeting and to welcome Dr Gray's widow, Mrs Frey Gray, to this opening session.

## References

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